

Drug Prescribing for the Elderly

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Age-related biologic and physiologic changes, the accumulation of multiple pathologic conditions with increasing age and several socioeconomic considerations combine to make drug prescribing for the elderly one of the most challenging tasks in clinical medicine. Numerous studies in older persons have documented alterations in the pharmacology of many drugs. Several general recommendations are presented which should make drug prescribing for elderly patients safer and more effective.

PRESCRIPTION MEDICATIONS represent a substantial portion of this country's ever-growing health care expenditures. They are not covered by many insurance plans for the elderly, and this can cause considerable out-of-pocket expense from what is often a fixed and limited income.

It is not unusual that several different drugs are prescribed for an elderly patient, to be taken on complex dosage schedules. This is especially so in acute care hospitals, where Medicare patients receive an average of ten prescription drugs,¹ and in nursing homes, where many of the four to seven drugs prescribed for each patient are inappropriate or ineffective.²

Drugs are a major cause of iatrogenic illnesses, conditions which are disturbingly common.^{3,4} One recent study found an iatrogenic illness in more than a third of patients on the medical service of a university hospital,⁴ and drugs were one of the most important factors in the development of these complications. Older persons are particularly susceptible to adverse drug reactions; the incidence of adverse reactions in hospitals increases from

3 percent in those aged 10 to 30⁵ to close to 25 percent in those older than age 80.⁶ These reactions contribute to more than 10 percent of admissions to geriatric departments in Great Britain,⁷ and account for as many as 3 percent of all admissions to US hospitals.⁸ As much as \$3 billion per year may be spent in this country as a result of adverse drug reactions.²

Given these costs, in both health and dollars, physicians should become aware of some of the complex considerations that attend prescribing for the elderly. Age-related biologic and physiologic changes, the accumulation of multiple pathologic conditions with increasing age and several socioeconomic factors combine to make prescribing drugs one of the most difficult, yet challenging, aspects of caring for these patients.

This article will briefly review age-related changes that are relevant to drug prescribing, and make several recommendations which are designed to make treatment of the elderly with drugs safer and more effective.

Age-Related Changes Relevant to Drug Prescribing

Altered Reporting and Presentation of Illness

Altered reporting and presentation of illness can make accurate diagnosis, and therefore appropriate drug prescription, more difficult in

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elderly patients. Impairments of hearing and vision, dementia and depression can all compromise a patient's ability to communicate symptoms. Vague and multiple somatic symptoms, extremely common in the elderly, often represent psychic distress rather than physical illness.⁹ Interpretation of these symptoms for physical illness, or exacerbation of an underlying medical condition, can result in inappropriate drug treatment.

Even when physical illnesses are present, they may be difficult to diagnose. Confusion, falls and urinary incontinence may be the presenting manifestations of a variety of treatable disorders; conditions such as hyperthyroidism and myocardial infarction may present with vague or nonspecific symptoms. As a result, treatable conditions can go unrecognized in this population.^{10,11} Left unrecognized, these disorders will not only remain untreated but may be exacerbated by drug treatment, or may alter the success of drug treatment for another illness.

Age-Related Biologic and Physiologic Changes

Age-related changes occur in many biologic and physiologic functions.¹² Table 1 lists several types of changes that can affect the pharmacology of many drugs.

It is crucial to keep in mind two characteristics of changes that occur with age. First, the changes are gradual and occur over many years. Second, there is wide interindividual variation in the rate of these age-related changes. Thus, although advancing age is associated with the decline in many physiologic functions, the extent of decline in any individual person is difficult to predict. This is important to remember when prescribing drugs; applying average age-related changes in physiologic functions to a particular older patient can be misleading, and may result in overdosage, as well as underdosage, of many drugs.

Absorption. As shown in Table 1, there are several age-related changes that could affect the absorption of drugs in the elderly.¹³ Although several studies of drug absorption in this population have been carried out,¹⁴ none have shown clinically meaningful changes. Altered absorption of drugs, therefore, appears to be the least important of age-related changes in pharmacology.

Distribution. Several changes related to age can affect the distribution of drugs. Alterations in blood flow, especially to the major sites of drug elimination (liver, kidney) can have important influences on drug kinetics and effects.¹⁵ Changes

TABLE 1.—*Age-Related Changes Relevant to Pharmacology*

<i>Age-Related Change</i>	<i>Pharmacologic Function</i>
Decreased absorptive surface	Absorption
Decreased splanchnic blood flow	
Increased gastric pH	
Altered gastrointestinal motility	Distribution
Decreased lean body mass	
Decreased total body water	
Decreased serum albumin	
Increased fat	
Altered protein binding	Hepatic metabolism
Decreased liver mass	
Decreased liver blood flow	
Decreased enzyme activity and inducibility	
Decreased renal blood flow	Renal excretion
Decreased glomerular filtration rate	
Decreased tubular secretory function	
Alterations in	Receptor sensitivity
Receptor number	
Receptor affinity	
Second messenger function	
Cellular responses	

in body composition, such as increased fat and decreased extracellular fluid and lean body mass,¹⁶ can alter the concentration and kinetics of drugs that distribute in the various body compartments. Decline in serum albumin,¹⁷ the major drug binding protein, can make more free drug available for pharmacologic action. The combination of lower serum albumin and polypharmacy may result in many adverse drug interactions—especially involving those drugs that are highly protein bound, such as salicylates, anticoagulants and orally given hypoglycemics.

Hepatic Metabolism. Although there are no age-related changes in routine liver function tests, the liver's capacity to metabolize drugs is altered with increasing age. Because blood flow to the liver declines,¹⁵ first-pass hepatic extraction and metabolism of orally administered drugs is diminished. The ability of environmental factors, such as cigarette smoking, to induce drug metabolizing enzymes decreases with age.¹⁸⁻²⁰ Studies of age-related changes in specific hepatic drug metabolic pathways, such as oxidation, hydroxylation and acetylation, have shown variable results.^{14,21,22} The effects of aging on hepatic drug metabolism are therefore complex, dependent on several factors and often difficult to predict.

Excretion. Several structural and functional changes occur in the kidney with increasing age²³ that have important influences on the excretion of drugs and their active metabolites (Table 1).

Because lean body mass declines with age, daily

TABLE 2.—*Important Considerations in Prescribing for the Elderly**

<i>Drugs</i>	<i>Pharmacokinetic Considerations</i>	<i>Other Considerations</i>
ANALGESICS		
Nonnarcotic	Aspirin may have longer duration of action and half-life may be prolonged at higher doses.	Aspirin, nonsteroidal antiinflammatory agents and acetaminophen generally of equivalent efficacy; latter may be less toxic. Salicylate blood levels may be helpful.
Narcotic	Morphine blood levels higher and duration of pain relief longer.	Lower doses of most narcotics may give adequate analgesia and less central nervous system and respiratory depression.
ANTIMICROBIALS		
	Penicillins (except nafcillin), aminoglycosides, cephalosporins, tetracyclines (except doxycycline) eliminated predominantly by kidney and may have prolonged half-lives and higher steady-state blood levels.	Aminoglycoside blood levels helpful. Isoniazid toxicity increases with age. Intravenous carbenicillin gives substantial sodium load.
CANCER CHEMOTHERAPY		
CARDIOVASCULAR AGENTS		
Antiarrhythmics	Lidocaine has increased volume of distribution and prolonged half-life. Quinidine and procainamide have prolonged half-lives and higher steady-state blood levels.	Lidocaine, quinidine and procainamide blood levels helpful. Disopyramide may have prominent anticholinergic effects, especially blurry vision and urinary retention. Lidocaine may cause confusion at high doses. Lower doses of warfarin needed for anticoagulation. Bleeding complications may be more frequent.
Anticoagulants		Sodium restriction and weight reduction may be effective when practical.
Antihypertensives		Elderly predisposed to dehydration and electrolyte imbalance.
Diuretics		Thiazides and furosemide may exacerbate glucose tolerance. Potassium sparing agents (or supplementation) necessary in some (especially with digoxin), but may cause hyperkalemia in others.
Other agents	Propranolol has prolonged half-life and higher blood levels. Metoprolol may have higher blood levels. Clonidine and methyldopa eliminated predominantly by kidney and may have prolonged half-life.	Propranolol often effective despite possible diminished sensitivity to cardiac effects. Incidence of adverse reactions higher, especially in patients with heart failure, bronchospasm, bradycardia or heart block, and those receiving hypoglycemic agents. Hydralazine may not cause reflex tachycardia but may exacerbate angina in some. Postural hypotension occurs in many even before therapy. Clonidine and prazosin usually do not cause postural hypotension with chronic therapy.
Digoxin	May have prolonged half-life and higher steady-state blood levels.	Blood levels helpful. May not be efficacious in chronic stable heart failure with sinus rhythm.
PSYCHOACTIVE AGENTS		
Antidepressants	Amitriptyline, imipramine and lithium may have higher blood levels.	Desipramine has the least anticholinergic and sedative effects. All tricyclics can cause postural hypotension; should be used carefully when antihypertensives have been prescribed. Doxepin may have less cardiotoxicity. Tricyclic blood levels may be helpful.

*After Ouslander JG: Drug Therapy in the Elderly. *Annals of Internal Medicine*, in press.

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TABLE 2.—Important Considerations in Prescribing for the Elderly (Continued)

Drugs	Pharmacokinetic Considerations	Other Considerations
Antipsychotic		Lithium blood levels important to avoid toxicity. Lower doses of phenothizines and haloperidol generally effective and safer.
Sedative/hypnotic	... Diazepam has prolonged half-life, especially in men. Oxazepam and lorazepam kinetics unchanged, and have shorter half-lives than other benzodiazepines.	Complaints of sleep disturbance may represent age-related changes in sleep patterns. Nonpharmacologic measures often effective for sleep disturbances. Increased sensitivity to effects of diazepam. Flurazepam more toxic in doses over 15 mg. Chloral hydrate generally safe and effective in doses up to 1 gram. Diphenhydramine may increase confusion in some.
OTHER DRUGS		
Aminophylline Less needed by intravenous infusion for therapeutic blood levels; half-life may be prolonged.	Blood levels helpful.
Cimetidine Half-life may be prolonged and steady-state blood levels higher.	May cause confusion at higher doses.
Hypoglycemic agents	. Eliminated predominantly by kidney (except chlorpropamide); tolbutamide has shortest half-life and may be cleared more rapidly; acetohexamide and tolazamide have intermediate duration of action (close to 24 hours).	Chlorpropamide may cause hyponatremia and prolonged hypoglycemia and is not generally indicated. Intermediate-acting drugs probably first choice given once per day.
Levodopa		Routine doses may cause confusion and postural hypotension.
Phenytoin Steady-state blood levels may be higher.	Blood levels helpful.
Thyroxine Metabolic clearance may be prolonged.	Maintenance dose may be lower. Thyroid stimulating hormone level helpful in following response.

endogenous creatinine production declines. Serum creatinine may therefore be "normal" in an elderly person, and may not reflect a substantial decline in creatinine clearance. Glomerular filtration rate declines an average of 35 percent between the ages of 20 and 90.²⁴ Formulae and nomograms have been developed to estimate true creatinine clearance in relation to age.^{25,26} One such formula is shown below:

$$\text{creatinine clearance} = \frac{(140 - \text{age}) \times \text{body wt (kg)}}{72 \times \text{serum creatinine}}$$

This result should be multiplied by 0.85 for women.²⁶

This formula can be useful to determine initial doses of drugs that are eliminated predominantly by renal excretion (such as aminoglycosides, cephalosporins, digoxin and procainamide).

Because of the interindividual variation in these age-related changes, and factors such as dehydration and heart failure which are often present in ill elderly patients, determinations of creatinine

clearance and blood drug levels may be more useful when available.

Receptor Sensitivity. It is often stated that old persons are more sensitive to drug effects. Recent studies of several drugs have shown age-related pharmacodynamic changes (altered drug effects that cannot be explained by pharmacokinetic changes). The elderly appear to be more sensitive than younger persons to the effects of given blood levels of diazepam²⁷ and warfarin,²⁸ yet less sensitive to the cardiac effects of isoproterenol and propranolol.²⁹ Although there are several potential mechanisms for these observations (Table 1), further research is necessary to more precisely define the underlying bases for these changes.

Pharmacology of Specific Drugs in the Elderly

Numerous studies have documented changes in the pharmacokinetics of many drugs in the elderly. It is beyond the scope of this review to describe these studies in detail; the reader is referred to

several recent reviews and texts that discuss these studies in depth.^{14,30-34}

Despite the large number of studies that have been done, it is difficult to make specific recommendations as to how to alter drug dosages for individual elderly patients. Several factors make the development of guidelines, such as those available for altering drug dosages in renal failure,³⁵ very complex. These factors include the wide interindividual variation of age-related changes, the coexistence of multiple conditions, the variability of the clinical status of individual elderly patients and the technical difficulties involved in defining age-related pharmacokinetic changes.³⁶

Table 2 and the discussion below briefly summarize pharmacologic information that is particularly relevant to the prescription of specific drugs for the elderly.

Analgesics

Many elderly persons frequently complain of pain. It is important to attempt to differentiate pain from an inflammatory process from noninflammatory causes, because the former may respond more favorably to aspirin and nonsteroidal inflammatory drugs. These drugs are of generally equivalent efficacy; the half-life of aspirin is increased in older persons, and may be greatly increased at higher doses. Determinations of salicylate blood levels may be helpful when high doses are used. Acetaminophen is safe in the elderly; it should be kept in mind that many patients with minor pain may benefit by nonpharmacologic treatments.

Narcotic analgesics appear to give more pain relief, and may have prolonged duration of action, in older patients.³⁷ These drugs can cause sedation, confusion and severe constipation (which can lead to fecal impaction and its attendant problems) in the elderly; the need for these drugs should be carefully assessed, therefore, and their use closely monitored.

Antimicrobials

Most antimicrobial drugs are eliminated predominantly by renal excretion (Table 2). Age-related changes in renal function should not influence the standard dosages of most of these drugs; aminoglycosides, because of their potential for ototoxicity and nephrotoxicity, should be used carefully. Blood level determinations may be useful when using these agents.

Two antimicrobial agents may have special potential for adverse reactions in old persons. Intravenously administered carbenicillin delivers a substantial sodium load, and should be used carefully in patients with symptomatic congestive heart failure. Isoniazid hepatotoxicity increases with age and its use should be carefully evaluated and monitored.³⁸

Cancer Chemotherapy

A recent analysis of data from the Eastern Cooperative Oncology Group showed that toxicity from protocols for lung, breast and colon cancer does not increase in the elderly.³⁹ This was true despite the lack of any dosage reductions; the regimens also were equally effective in the older age groups.

Cardiovascular Agents

Antiarrhythmics. Arrhythmias are common in the elderly, but because of the potential toxicity of antiarrhythmic agents, the necessity for treatment should be carefully evaluated. Lidocaine, quinidine and procainamide all have prolonged half-lives in the elderly; the latter two drugs also have higher steady-state blood levels.^{40,41} Blood levels of these agents can be helpful in monitoring therapy. Disopyramide can cause prominent anticholinergic side effects in these patients, such as urinary retention and blurry vision. Other newer antiarrhythmics have not been well studied in older persons.

Antihypertensives. The management of hypertension in the elderly remains controversial.^{42,43} Although data are scarce in the very old (older than 75), recent studies involving persons between 60 and 69 years of age indicate that hypertension remains an important risk factor for cardiovascular morbidity and mortality,^{44,45} and that treatment may reduce this risk.⁴⁶

Antihypertensives may, however, produce serious adverse reactions in the elderly. Diuretics may predispose to electrolyte imbalance and dehydration, especially when an intercurrent illness decreases oral intake. They may also exacerbate urinary incontinence. Postural hypotension is common even without drugs, and may be exacerbated by most antihypertensive agents. This may lead to falls and their sequelae; lethargy, depression and confusion may also result from antihypertensive agents.

β -Adrenergic blocking agents, although useful for hypertension as well as angina, must be used

carefully in the elderly. The incidence of adverse reactions is higher,⁴⁷ especially with chronic obstructive lung disease, congestive heart failure, bradycardia and concurrent hypoglycemic therapy. Although there is some evidence that old persons are less sensitive to the cardiac effects of propranolol,²⁹ its metabolism is diminished, half-life prolonged and blood levels higher.^{19,48}

The potential benefits of antihypertensive therapy must be carefully weighed against the possible adverse effects on the quality of life. Restrictive diets, although helpful in some, may be unpalatable and impractical for many elderly persons. The reader is referred to recent reviews for more detailed suggestions on the management of hypertension in this population.^{42,43}

Digoxin. Digoxin is one of the most frequently prescribed yet potentially toxic drugs in the elderly.^{7,31} Recent studies have suggested that persons with chronic heart failure in sinus rhythm can be safely withdrawn from therapy,^{49,50} although this remains controversial.⁵¹ Because of its potential toxicity, the necessity for this agent should be carefully evaluated (it should not be given for nonspecific symptoms alone, such as fatigue, dyspnea or lower extremity edema). Blood levels may be helpful in determining compliance and toxicity. Toxicity may be especially difficult to diagnose because the manifestations are often nonspecific (such as fatigue and weakness).⁵²

Psychoactive Drugs

Despite considerable evidence that psychoactive drugs have enhanced toxicity in older persons,⁵³⁻⁵⁵ they are commonly used in this population; 75 percent of nursing home residents receive at least one of these drugs and usually more.⁵⁶

Although the judicious use of these drugs can provide dramatic relief of the anxiety, agitation and depression so common in the elderly, it should be remembered that these symptoms may reflect underlying physical illness.⁸ Excessive sedation may result from many of these drugs, especially hypnotics such as flurazepam (when given in doses of 30 mg or more).⁵⁵ Many of these agents have prominent anticholinergic effects (especially amitriptyline, doxepin, thiorazine and thioridazine) and can cause confusion, blurry vision, urinary retention and constipation. Tricyclic antidepressants can cause postural hypotension (especially when added to an antihypertensive agent) and falls, as well as prolonged cardiac conduction.

They must be used very carefully in older patients with underlying cardiovascular disease.⁵⁷ Many of these drugs (especially antipsychotic drugs such as haloperidol and thioridazine) can have prominent extrapyramidal side effects, and can exacerbate underlying Parkinson's disease and other gait disturbances in these patients.

Although numerous drugs have been used to improve cognitive function in the elderly, none have been shown in rigorously controlled studies to have substantial impact on daily functional capabilities. Until further research yields better drugs, these agents (which are often very expensive) should not replace careful evaluation and follow-up of cognitive impairment, and counseling of the patient and family.

The reader is referred to recent comprehensive reviews that deal in depth with psychoactive drug use in the elderly.^{32,58}

Other Drugs

Important considerations for other commonly used drugs in the elderly, such as aminophylline, cimetidine and oral hypoglycemic agents are shown in Table 2.

Compliance

Compliance is often a major obstacle to drug treatment in any population. Most studies show between a third and a half of patients will fail to comply with a medical regimen.⁵⁹

Several factors make compliance an even more complex feature of drug prescribing in the elderly. Mild and chronic disorders that require prophylactic or suppressive therapy, and in which the consequences of stopping therapy may be delayed, lend themselves to noncompliance. Complex medical regimens, requiring several different medications and frequent doses, may also contribute to a higher incidence of noncompliance. All of these are common in the elderly population.

In addition to the prevalence of multiple chronic illnesses and the attendant need for complex drug regimens, a variety of physical, psychological, social and economic barriers may impair an older patient's ability to comply.

The average elderly person in this country spends more than \$100 a year on prescription drugs,⁶⁰ and these costs, usually not well covered by reimbursement plans, come out of an already fixed and limited income. Intellectual impairment, poor vision and diminished hearing may make patient education difficult, and prevent a patient

from following instructions. Many older persons have cultural attitudes and beliefs that may make the process even harder. Weakened, arthritic hands are often unable to open childproof containers, and this may be a problem in as many as 60 percent of elderly patients.⁶¹ Lack of transportation or fear of crime may prevent the elderly from reaching a physician or pharmacist.

Many studies emphasize the need for careful supervision of elderly patients requiring long-term medication.^{62,63} One of these showed that teaching a patient an individual drug regimen in the hospital may help identify and overcome problems with noncompliance.⁶⁴ Instructional aids such as tablet identification cards and tear-off calendars have also been shown to improve compliance in these patients.⁶⁴

Recommendations

Although nomograms for specific dosage adjustments in the elderly have not been (and may never be) developed, there are several recommendations, shown in Table 3, that should be

TABLE 3.—General Recommendation for Prescribing for the Elderly*

- Evaluate elderly patients for previously undiagnosed and treatable conditions that may affect, or be affected by drug therapy.
- Manage conditions without drugs as often as possible.
- Avoid interactions between newly prescribed drugs, drugs already being taken and underlying conditions.
- If there is any question about dosage, start with smaller doses and increase gradually.
- For drugs or their active metabolites eliminated predominantly by the kidney, formulae can be used to approximate age-related decline in renal function, and dosages adjusted accordingly.
- For drugs predominantly eliminated by hepatic metabolism, age-related changes are variable and difficult to predict in the absence of overt liver disease.
- Blood levels can be helpful in monitoring several potentially toxic drugs frequently used in the elderly.
- Individually tailor and simplify the drug regimen as much as possible.
- Pay special attention to impaired intellect, poor vision and diminished hearing when educating the patient and labeling the prescriptions.
- Help ensure compliance by asking if the patient has access to a pharmacy, can afford the prescription and can open the containers.
- Make use of relatives, friends, visiting health professionals and local pharmacists in helping the patient to comply.
- Monitor the patient frequently for compliance, drug effects and toxicity.

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helpful in making drug prescribing safer and more effective. Special emphasis is placed in these recommendations on careful evaluation of the need for, and monitoring of, drug treatment; as well as the nonpharmacologic and socioeconomic aspects of drug prescribing for this population. In many instances, the latter considerations are more important to the efficacy of such drug prescribing than age-related changes in drug pharmacology.

Summary

Many age-related biologic and physiologic changes can have important influences on drug pharmacology in elderly patients. Although numerous studies have been done, interindividual variation in the rates of age-related changes, differences in the clinical status of individual patients and technical difficulties in carrying out pharmacokinetic studies make it difficult to give specific recommendations for drug prescribing in older patients. Many socioeconomic and other nonpharmacologic factors have important influences on prescribing for this population.

Several general recommendations have been presented which should be helpful in prescribing for the elderly. As we gain more experience caring for this rapidly growing segment of our population, we are sure to achieve new insights into the complex and challenging task of safe and effective drug prescribing.

REFERENCES

1. Nitham CJ, Parkhurst YE, Sommers EB: Physicians prescribing habits: Effects of Medicare. *JAMA* 217:585-587, 1971
2. Subcommittee on Aging and Subcommittee on Long Term Care—U.S. Senate Special Committee on Aging: *Drugs in Nursing Homes: Misuse, High Cost, and Kickbacks*. Supporting Paper No. 2. Washington, DC, U.S. Government Printing Office, 1976
3. Kane RL: Iatrogenesis: Just what the doctor ordered. *J Community Health* 5:149-158, 1980
4. Steel K, Gertman PM, Crescenzi C, et al: Iatrogenic illness on a general medical service at a university hospital. *N Engl J Med* 304:638-642, 1981
5. Hurwitz M: Predisposing factors in adverse reactions to drugs. *Br Med J* 1:536-539, 1969
6. Seidel LG, Thornton GF, Smith JW, et al: Studies on the epidemiology of adverse drug reactions—III. Reactions in patients on a general medical service. *Bull Johns Hopkins Hosp* 119:299-315, 1966
7. Williamson J, Chopin JM: Adverse reactions to prescribed drugs in the elderly: A multicentre investigation. *Age Ageing* 9: 73-80, 1980
8. Caranasos GJ, Stewart RB, Cluff LE: Drug-induced illness leading to hospitalization. *JAMA* 288:713-717, 1974
9. Salzman C, Shader RI: Clinical evaluation of depression in the elderly. In Raskin A, Jarvik LF (Eds): *Psychiatric Symptoms and Cognitive Loss in the Elderly*. New York, Hemisphere Publ Co, 1979, pp 39-72
10. Williams TF, Hill JG, Fairbank ME, et al: Appropriate placement of the chronically ill aged—A successful approach by evaluation. *JAMA* 226:1332-1335, 1973
11. Brocklehurst JC, Carty MH, Leeming JT, et al: Medical screening of old people accepted for residential care. *Lancet* 1: 141-142, 1978
12. Finch CE, Hayflick L (Eds): *Handbook of the Biology of Aging*. New York, Van Nostrand Reinhold Co, 1977
13. Bender AD: Effect of aging on intestinal absorption: Implications for drug absorption in the elderly. *J Amer Ger Soc* 16:1331-1339, 1968

14. O'Malley K, Laher M, Cusack B, et al: Clinical pharmacology and the elderly patient, *In* Denham MJ (Ed): *The Treatment of Medical Problems in the Elderly*. Baltimore, University Park Press, pp 7-9, 1980
15. Bender AD: The effect of increasing age on the distribution of peripheral blood flow in man. *J Amer Ger Soc* 13:192-198, 1965
16. Norris AH, Lundy T, Shock NW: Trends in elected indices of body composition in men between the ages of 30 and 80 years. *Ann NY Acad Sci* 110:623-639, 1963
17. Wallace S, Whiting B, Runcie J: Factors affecting drug binding in plasma of elderly patients. *Br J Clin Pharmacol* 3:327-330, 1976
18. Adelman RC: Age-dependent effects in enzyme induction—A biochemical expression of aging. *Exp Gerontol* 6:75-87, 1971
19. Vestal RE, Wood AJ, Branch RA, et al: Effects of age and cigarette smoking on propranolol disposition. *Clin Pharm Ther* 26:8-15, 1979
20. Wood AJJ, Vestal RE, Wilkinson GR, et al: Effect of aging and cigarette smoking on antipyrine and indocyanine green elimination. *Clin Pharm Ther* 26:16-20, 1979
21. Farrah F, Taylor W, Rawlins MD, et al: Hepatic drug acetylation and oxidation: Effect of aging in man. *Br Med J* 2:155-156, 1977
22. Ritschel WA: Age-dependent disposition of amobarbital: Analog computer evaluation. *J Amer Ger Soc* 12:540-543, 1978
23. Epstein M: Effects of aging on the kidney. *Fed Proc* 38:168-172, 1979
24. Rowe JW, Andres R, Tobin JD, et al: The effect of age on creatinine clearance in man: A cross-sectional and longitudinal study. *J Geront* 31:155-163, 1976
25. Kampmann J, Siesbaek-Nielsen K, Kristensen M, et al: Rapid evaluation of creatinine clearance. *Acta Med Scan* 196:517-520, 1974
26. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31-41, 1976
27. Reidenberg MM, Levy M, Warner H, et al: Relationship between diazepam dose, plasma level, age and central nervous system depression. *Clin Pharm Ther* 23:371-374, 1978
28. Shepherd AM, Hewick DS, Moreland TA, et al: Age as a determinant of sensitivity to warfarin. *Br J Clin Pharm* 4:315-320, 1977
29. Vestal R, Wood AJJ, Shand DG: Reduced beta-adrenoceptor sensitivity in the elderly. *Clin Pharm Ther* 26:818-886, 1979
30. Jarvik LF, Greenblatt D, Harman D (Eds): *Pharmacology and the Aged Patient*. New York, Raven Press, 1981
31. Lamy PP: *Prescribing for the Elderly*. Littleton, MA, PSG Publishing Co, 1980
32. Hicks R, Funkenstein HH, Dysken MW, et al: Geriatric psychopharmacology, *In* Birren J, Sioane RB (Eds): *Handbook of Mental Health and Aging*. Englewood Cliffs, NJ, Prentice Hall, 1980, pp 745-774
33. Richey DP, Bender AD: Pharmacokinetic consequences of aging. *Ann Rev Pharm Tox* 17:49-65, 1977
34. Vestal RE: Drug use in the elderly. A review of problems and special considerations. *Drugs* 16:358-382, 1978
35. Bennett WM, Muther RS, Parker, RA, et al: Drug therapy in renal failure: Dosing guidelines for adults. *Ann Int Med* 93:62-89, 286-325, 1980
36. Greenblatt DJ, Shader RI: Pharmacokinetics in old age: Principles and problems of assessment, *In* Jarvik LF, Greenblatt DJ, Harman D (Eds): *Pharmacology and the Aged Patient*. New York, Raven Press, 1981, pp 27-46
37. Bellville JW, Forrest WH, Miller E, et al: Influence of age on pain relief from analgesics—A study of postoperative patients. *JAMA* 217:1835-1841, 1971
38. Baily WC, Weill H, Derowen TA, et al: The effect of isoniazid on transaminase levels. *Ann Int Med* 81:200-202, 1974
39. Begg CB, Cohen JL, Ellerton J: Are the elderly predisposed to toxicity from cancer chemotherapy?—An investigation using data from the Eastern Cooperative Oncology Group. *Cancer Clin Trials* 3:369-374, 1980
40. Reidenberg MM, Bamacho M, Kluger J, et al: Aging and renal clearance of procainamide and acetylprocainamide. *Clin Pharm Ther* 28:732-735, 1980
41. Ochs RH, Greenblatt DJ, Woo E, et al: Reduced quinidine clearance in elderly persons. *Am J Cardiol* 42:481-485, 1978
42. Kirkendall WM, Hammond JJ: Hypertension in the elderly. *Arch Int Med* 140:1155-1161, 1980
43. O'Malley K, O'Brien E: Management of hypertension in the elderly. *N Engl J Med* 302:1397-1401, 1980
44. Veterans Administration Cooperative Study Group on Anti-hypertensive Agents: Effects of treatment on morbidity in hypertension—III. Influence of age, diastolic pressure, and cardiovascular disease—A further analysis of side effects. *Circulation* 45:991-1004, 1972
45. Kannel WB, Gordon T: Evaluation of cardiovascular risk in the elderly—The Framingham Study. *Bull NY Acad Med* 54:573-591, 1979
46. Hypertension Detection and Follow-up Program Cooperative Group: Five-year findings of the hypertension detection and follow-up program—I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA* 242:2562-2576, 1979
47. Greenblatt DJ, Kock-Weser J: Adverse reactions to propranolol in hospitalized medical patients: A report from the Boston Collaborative Drug Surveillance Program. *Am Heart J* 86:478-484, 1973
48. Castelden CM, George CF: The effect of age on the hepatic clearance of propranolol. *Br J Clin Pharmacol* 7:49-54, 1979
49. Johnston GD, McDewitt DG: Is maintenance digoxin necessary in patients with sinus rhythm? *Lancet* 1:567-570, 1979
50. McHaffie D, Purcell H, Mitchell-Heggs P, et al: The clinical value of digoxin in patients with heart failure and sinus rhythm. *Q J Med* 47:401-419, 1978
51. Arnold SB, Byrd RC, Meister W, et al: Long-term digitalis therapy improves left ventricular function in heart failure. *N Engl J Med* 303:1443-1448, 1980
52. Lely AH, Van Enter CHJ: Large-scale digitoxin intoxication. *Br Med J* 1:737-740, 1970
53. Davies RK: Confusional episodes and antidepressant medication. *Am J Psychiatry* 128:95-99, 1971
54. Boston Collaborative Drug Surveillance Program: Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *N Engl J Med* 288:277-280, 1973
55. Greenblatt DJ, Allen MD, Shader RI: Toxicity of high dose flurazepam in the elderly. *Clin Pharm Ther* 21:355-361, 1977
56. Special Committee on Aging, United States Senate: *Nursing Home Care in the United States: Failure in Public Policy*. Washington, DC, Government Printing Office, 1974
57. Risch SC, Groom GP, Janowsky DS: Interfaces of psychopharmacology and cardiology—Parts One and Two. *J Clin Psychiat* 42:23-34, 47-59, 1981
58. Jarvik LF, Kakkar PR: Aging and response to antidepressants, *In* Jarvik LF, Greenblatt DJ, Harman D (Eds): *Pharmacology and the Aged Patient*. New York, Raven Press, 1981
59. Haynes RB, Taylor DW, Sackett DL (Eds): *Compliance in Health Care*. Baltimore: The Johns Hopkins University Press, 1979
60. National Center for Health Statistics: *Health Interview Survey, U.S. 1975*. DHEW Publication No. (HRA) 77-1543, Rockville, MD, 1977
61. Sherman FT, Warach JD, Libow LS: Child resistant containers for the elderly? (Editorial). *JAMA* 241:1001-1002, 1979
62. Adkinson L, Gibson I, Andrews J: An investigation into the ability of elderly patients to take prescribed drugs after discharge from hospital and recommendations concerning improving the situation. *Gerontology* 24:225-234, 1978
63. Libow LS, Mehl B: Self-administration of medications by patients in hospitals or extended care facilities. *J Amer Ger Soc* 18:81-95, 1970
64. Wandless I, Davie JW: Can drug compliance in the elderly be improved? *Br Med J* 1:359-361, 1977